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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/553,108 | 10/12/2005 | Nobuo Mochizuki | 20241/0203481-US0 | 8647 |

7278 7590 07/23/2009

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| EXAMINER | |
|---|---|
| HAVLIN, ROBERT H | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1626 | |

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|---|---|
| 07/23/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/553,108 | MOCHIZUKI ET AL. | |
| | Examiner | Art Unit | |
| | ROBERT HAVLIN | 1626 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,5 and 13-20* is/are pending in the application.

4a) Of the above claim(s) *16 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,13-15,17,18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

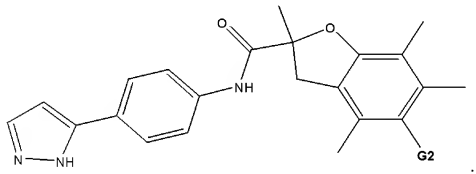
**Status of the claims:** Claims 1, 3, 5, and 13-20 are currently pending. Claims 2, 4, and 6-12 have been cancelled. Claims 15-20 were newly presented.

**Priority:** This application is a 371 of PCT/JP04/05237 04/13/2004 and claims foreign priority to JAPAN 2003-109667 (04/14/2003) and JAPAN 2004-023032 (01/30/2004).

### *Election/Restrictions*

1. Applicant previously elected Group I (claims 1-3, 5, 6, and 13) in the reply filed on 9/19/07.

Applicant also elected the species of Compound 37 reading on claims 1-3, 5, 13, and 14 with the following structure (G2=NH2):

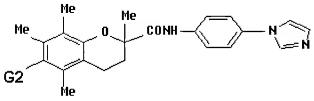



As detailed below, the generic claim was found unpatentable and in accordance with the election of species practice described in the requirement for restriction, subject matter not reading on the elected species is hereby withdrawn. Accordingly, claims 16 and 19 are hereby withdrawn.

### *Declaration*

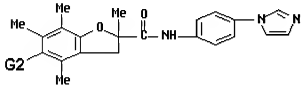
2. The declaration under 37 CFR 1.132 filed 5/1/2009 by Seiichi Uchida is considered below.

The declaration compares "Compound 2" of the instant application (G2 is NH2) with the prior art "Compound 3-1" of the '516 patent (G2 is OH) having the following structure:




with "inhibition rate of ex vivo lipid peroxide action in the brain (%)" activities of 97± 0.9 % and 45 ± 21.0 % respectively.

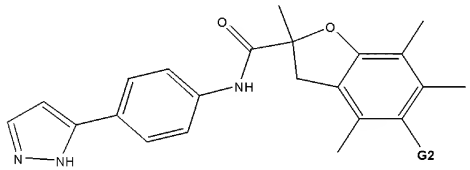
The declaration also compares "Compound 1" of the instant application (G2 is NH2) with the prior art "Compound 3-9" of the '516 patent (G2 is OH) having the following structure:




with "inhibition rate of ex vivo lipid peroxide action in the brain (%)" activities of 83± 12.1 % and 22 ± 31.5 % respectively.

The above comparisons are persuasive as to the non-obviousness with respect to the particular compounds for the activities compared. However, as is detailed in the following rejections, this comparison is not persuasive as to the entire genus of compounds claimed because there is an obvious unpredictability in the art with respect to the activities of the compounds as demonstrated by the declarations already considered.

The earlier 9/24/08 declaration compared "Compound 37" of the instant application (G2 is NH2) with the prior art "Compound 3-19" of the '516 patent (G2 is OAc) having the following structure:




with "inhibition rate of ex vivo lipid peroxide action in the brain (%)" activities of 55±15.8 % and 19±20.6 % respectively (where the ± values are equal to two times the standard deviation).

**RESPONSE TO APPLICANT ARGUMENTS**

***Claim Objections***

1. Claims 2, 6, 13 and 14 were objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant has amended the claims such that the clams are now in proper dependent form. Accordingly, the objection is **withdrawn**.

***Claim Rejections - 35 USC § 112***

2. Claims 1-3, 5, 6, and 14 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Several of the claims have definitions

or use claim language precluding one of ordinary skill in the art from discerning the claim scope. Exemplary language is as follows:

- Claims 1 and 5 continue to use improper language, specifically in the definition of "R1" as "substituted." This definition remains open ended and provides no boundary to the definition of the structure. The examiner recommends including the specific alternative structure applicant intends to claim with this language.
- Claim 3 was amended to replace "benzene ring" with "phenyl group," however this does not cure the ambiguity. The examiner recommends including the language of "the phenyl group of formula (I)."

For the above reasons, **the rejection is maintained for claims 1, 3, and 5**.

***Claim Rejections - 35 USC § 103***

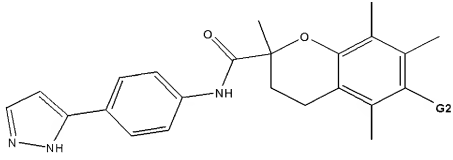
3. Claims 1-3, 5, 6, 13, and 14 were rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,342,516 ('516) in view of Patani et al. (Chem. Rev., 1996, Vol. 96, No. 8, P. 3147-3176).

Applicant alleges on page 11-12 of their remarks that the examiner indicated the subject matter directed to compounds where A is pyrazolyl was generally allowable.

As was stated in the Examiner's interview summary of March 25, 2008, the examiner agreed to reconsider the non-obviousness of the elected species and indicated claim 1 might be allowable if restricted to pyrazolyl derivatives *contingent on reexamination of the prior art*.

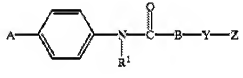
Accordingly, the examiner has reexamined the prior art and found that the claims remain obvious over the prior art.

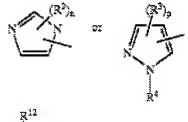
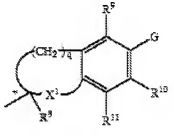
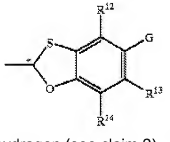
The instant claims read on the following compound (where G2 is NH2):




*1. Determining the scope and contents of the prior art.*

The '516 reference teaches a genus of compounds as a pharmaceutical agent for preventing peroxidized lipid production (col. 2, line 25) and also have antioxidation activity (col. 66, line 4). Specifically in claim 1 compounds of the following formula:

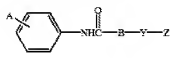



where A is:  ; and Z can be  or  wherein G can be –OR15 or NHR15 where R15 includes hydrogen (see claim 2).

'516 also teaches a number of specific compounds in table 3 in column 59:

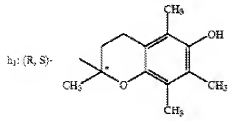
59

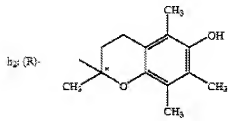
TABLE 3

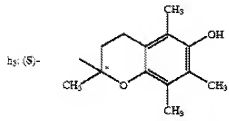


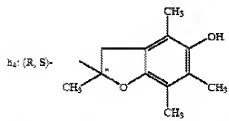
| Compound No | A* | B | Y | Z | Physical Constant [ ] m.p. ° C. |
|---|---|---|---|---|---|
| 3-1 | 4-a1 | — | — | $h_1$ | [229–231] |
| 3-2 | 4-a1 | — | — | $h_2$ | [219–222] |
| 3-3 | 4-a1 | — | — | $h_3$ | [220–222] |
| 3-4 | 4-a1 | $CH_2$ | — | $h_1$ | [126–129] |
| 3-5 | 4-a1 | $CH_2CH_2$ | — | $h_1$ | [112–114] |
| 3-6 | 4-a1 | $CH(Me)CH_2$ | — | $h_1$ | [137–142] |
| 3-7 | 4-a1 | $CH_2$ | $NMe_2C(=O)$ | $h_1$ | amorphous&NMR1 |
| 3-8 | 4-a1 | $(CH_2)_5$ | NHC(=O) | $h_1$ | [194–196] |
| 3-9 | 4-a1 | — | — | $h_4$ | [232–233] |
| 3-10 | 4-a1 | $CH_2CH_2$ | — | $h_4$ | [110–113] |
| 3-11 | 4-a1 | $CH_2CH_2$ | — | $h_5$ | [194–207] |
| 3-12 | 4-a1 | $(CH_2)_4$ | — | $h_1$ | [211–214] |
| 3-13 | 4-a1 | — | — | $h_9$ | [192–193] |
| 3-14 | 4-a1 | — | — | $h_6$ | [204–206] |
| 3-15 | 4-a1 | CH=CH | — | $h_1$ | [143–148] |
| 3-16 | 4-a1 | CH=CH—CH=CH | — | $h_4$ | [245–246] |
| 3-17 | 4-a1 | $(CH_2)_4$ | — | $h_1$ | [211–214] |
| 3-18 | 4-a1 | — | — | $h_{12}$ | [184–187] |
| 3-19 | 4-a2 | — | — | $h_6$ | [203–206] |
| 3-20 | 4-a1 | — | | $h_7$ | amorphous&NMR2 |
| 3-21 | 4-a1 | — | — | $h_1$ | [207–210] |
| 3-22 | 2-a1 | — | — | $h_1$ | [191–196] |
| 3-23 | 4-a3 | — | — | $h_1$ | [203–205] |
| 3-24 | 4-a5 | — | — | $h_1$ | [166–167] |
| 3-25 | 4-a2 | — | — | $h_1$ | [215–218] |
| 3-26 | 4-a2 | $CH_2CH_2$ | — | $h_6$ | [195–196] |
| 3-27 | 4-a1 | $(CH_2)_2CH(Ph)$ | | $h_{14}$ | amorphous&NMR3 |
| 3-28 | 4-a1 | $(CH_2)_2CH(Ph)$ | — | $h_{14}$ | amorphous&NMR4 |
| 3-29 | 4-a1 | $(CH_2)_4$ | — | $h_{14}$ | [140–143] |
| 3-30 | 4-a1 | $CH_2CH_2$ | — | $h_{14}$ | [145–150] |

Representing together the substitution site to the phenyl group.
& represents the NMR data are presented in Table 5.



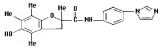



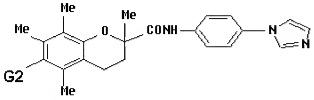




Me: methyl, Et: ethyl, Bu: butyl, Ph: phenyl
a1: 1-imidazole, a2:1H-pyrazol-5-yl,
a3: 1H-pyrazol-4-yl,
a4: 1-methylpyrazol-5-yl,
a5: 1-methylpyrazol-3-yl,

The reference also teaches the compounds discussed in the 132 declaration above including the compound 3-9

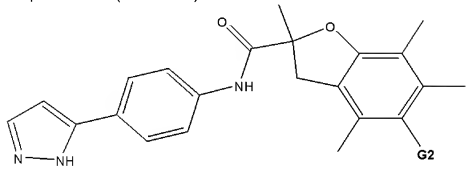


compound 3-1 (G2 is OH):

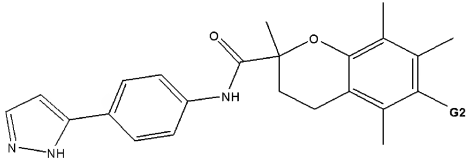



, and

Compound 3-19 (G2 is OAc):




The reference also teaches the species of "Compound 3-13" having the following formula (where G2 is OH):




Patani et al. teaches on pages 3152-54 the bioisosteric replacement of a hydroxyl group with an amino group while retaining activity. The reference teaches the application generally and also provides several specific examples in related contexts.

*2. Ascertaining the differences between the prior art and the claims at issue.*

The difference between the '516 compound and the claims is a hydroxyl instead of an amino substitution at the "G2" position.

*3. Resolving the level of ordinary skill in the pertinent art.*

One of ordinary skill in the art would be well versed in the well-known method of bioisosteric replacement to optimize pharmaceutical compounds. In addition, modifying the G2-position substitutent is a routine procedure well within the technical grasp of those of ordinary skill in the art.

*4. Considering objective evidence present in the application.*

The instant claims are encompassed by the claims of the '516 patent. One of ordinary skill in the art, upon reading the teaching of '516 and the specific teaching of the "G2" position as NH2 in claim 2 would immediately recognize through structural similarity and specifically the teaching of Patani that the '516 compound would have the desired antioxidant activity if the hydroxyl group were modified to an amino group. See MPEP 2144.09(II). In Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd., 87 USPQ2d 1452, 1454 (Fed. Cir. 2008), the Federal Circuit clarified the proof of obviousness in structural similarity situations such as this:

> Where, as here, the patent at issue claims a chemical compound, the analysis of the third Graham factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds. See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1377 [81 USPQ2d 1324] (Fed. Cir. 2006) (noting that, for a chemical compound, a prima facie case of obviousness

requires "structural similarity between claimed and prior art subject matter … where the prior art gives reason or motivation to make the claimed compositions" (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 [83 USPQ2d 1169] (Fed. Cir. 2007). In keeping with the flexible nature of the obviousness inquiry, KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739 [82 USPQ2d 1385] (2007), the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. See Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 [84 USPQ2d 1198] (Fed. Cir. 2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship … to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." Id. (quoting Dillon, 919 F.2d at 692).

Therefore, because the prior art teaches compounds with G2 as NH2 and because the species taught possesses a sufficiently close structural relationship to the instantly claimed compounds and Patani further suggests the compound will maintain activity with the specific modification, the claims remain obvious.

Specifically, **claims 1, 3, 5, 13-15, 17, 18, and 20 are rejected** under 35 U.S.C. 103(a) as being unpatentable over US 6,342,516 ('516) in view of Patani et al. (Chem. Rev., 1996, Vol. 96, No. 8, P. 3147-3176) for the aforementioned reasons.

***Conclusion***

3. No generic claim was held allowable, the claims are restricted to the elected species only and the remaining subject matter held withdrawn. The claims are not in condition for allowance. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT HAVLIN whose telephone number is (571)272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/
Examiner, Art Unit 1626